Impact of Diabetes Mellitus and Chronic Kidney Disease on Cardiovascular Outcomes and Platelet P2Y(12) Receptor Antagonist Effects in Patients With Acute Coronary Syndromes : Insights From the PLATO Trial

PLATO Investigators

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ORIGINAL RESEARCH

Impact of Diabetes Mellitus and Chronic Kidney Disease on Cardiovascular Outcomes and Platelet $P2Y_{12}$ Receptor Antagonist Effects in Patients With Acute Coronary Syndromes: Insights From the PLATO Trial

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***Background*—**There are limited data on how the combination of diabetes mellitus (DM) and chronic kidney disease (CKD) affects cardiovascular outcomes as well as response to different $P2Y_{12}$ receptor antagonists, which represented the aim of the present investigation.

***Methods and Results*—**In this post hoc analysis of the PLATO (Platelet Inhibition and Patient Outcomes) trial, which randomized acute coronary syndrome patients to ticagrelor versus clopidogrel, patients (n=15 108) with available DM and CKD status were classified into 4 groups: DM+/CKD+ (n=1058), DM+/CKD− (n=2748), DM−/CKD+ (n=2160), and DM−/CKD− (n=9142). The primary efficacy end point was a composite of cardiovascular death, myocardial infarction, or stroke at 12 months. The primary safety end point was PLATO major bleeding. DM+/CKD+ patients had a higher incidence of the primary end point compared with DM−/CKD− patients (23.3% versus 7.1%; adjusted hazard ratio 2.22; 95% CI 1.88–2.63; $P<0.001$). Patients with DM+/CKD− and DM−/CKD+ had an intermediate risk profile. The same trend was shown for the individual components of the primary end point and for major bleeding. Compared with clopidogrel, ticagrelor reduced the incidence of the primary end point consistently across subgroups (*P*-interaction=0.264), but with an increased absolute risk reduction in DM+/CKD+. The effects on major bleeding were also consistent across subgroups (*P*-interaction=0.288).

***Conclusions*—**In acute coronary syndrome patients, a gradient of risk was observed according to the presence or absence of DM and CKD, with patients having both risk factors at the highest risk. Although the ischemic benefit of ticagrelor over clopidogrel was consistent in all subgroups, the absolute risk reduction was greatest in patients with both DM and CKD.

***Clinical Trial Registration*—**URL: http://www.clinicatrials.gov. Unique identifier: NCT00391872. **(*J Am Heart Assoc*. 2019;8: e011139. DOI: 10.1161/JAHA.118.011139.)**

Key Words: acute coronary syndrome • chronic kidney disease • clopidogrel • diabetes mellitus • ticagrelor

Patients with diabetes mellitus (DM) are at increased risk of atherothrombotic events.[1] Importantly, DM is a key risk factor for the development of chronic kidney disease (CKD), a well-known cardiovascular risk factor.[2,3] These observations underscore the importance of antiplatelet therapy for secondary prevention of atherothrombotic

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An accompanying Appendix S1 is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.011139

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Clinical Perspective

What Is New?

- Acute coronary syndrome patients with diabetes mellitus and chronic kidney disease are at markedly increased risk for long-term atherothrombotic events compared with patients without these risk factors, as well as with those with only 1 of these.
- Although the ischemic benefit of ticagrelor versus clopidogrel was consistent in all patient subgroups, the magnitude of benefit was enhanced according to the patient risk profile.

What Are the Clinical Implications?

- There is a need to define the most effective treatment options for these high-risk patients, including strategies to reduce the risk of developing chronic kidney disease in patients with diabetes mellitus.
- Similarly, in patients with established chronic kidney disease, glucose control is also critical to reduce the risk of developing diabetes mellitus.
- Clinicians should use more potent platelet-inhibiting therapy in acute coronary syndrome patients with diabetes mellitus and chronic kidney disease who are often undertreated because of high perceived risk of bleeding.

recurrences in these high-risk patients. Dual antiplatelet therapy with aspirin and a $P2Y_{12}$ receptor inhibitor is the standard of care for secondary prevention in acute coronary syndrome (ACS) patients.[4] Guidelines recommend that the more potent $P2Y_{12}$ receptor inhibitors (ie, prasugrel or ticagrelor) be preferred over clopidogrel for the treatment of ACS patients because of their greater benefit in reducing the risk of cardiovascular events in these patients, albeit at the expense of increased bleeding.[4,5] Nevertheless, clopidogrel remains widely used in ACS patients.[6,7] DM patients treated with clopidogrel have increased rates of recurrent atherothrombotic events, which may be in part because of reduced platelet inhibitory effects of clopidogrel consistently observed among these subjects.[1,8–11] Although studies assessing the impact of CKD status on clopidogrel-induced antiplatelet effects have yielded conflicting findings, pharmacodynamic assessments conducted among DM patients have shown a greater magnitude of impaired clopidogrel-induced platelet inhibition among those with CKD compared with those without CKD.[12–19]

These observations, as well as those from other small observational studies, suggest that the concomitant presence of DM and CKD status can increase ischemic event rates, underscoring the need for more effective platelet-inhibiting therapies in these high-risk patients.[20,21] However, to date most large-scale studies assessing how the presence of DM and CKD affects cardiovascular outcomes and the relative impact of specific antiplatelet treatment regimens, in particular $P2Y_{12}$ receptor inhibitors, have considered these risk factors separately.[1,2] Indeed, the ever-growing prevalence of CKD in patients with DM underscores the need to better risk stratify these patient cohorts. The aim of this analysis was to assess clinical outcomes in ACS patients from the PLATO (Platelet Inhibition and Patient Outcomes) trial according to the presence or absence of DM and CKD, as well as the differential effects of $P2Y_{12}$-inhibiting therapies (ticagrelor versus clopidogrel) in these populations.

Methods

The PLATO trial (www.ClinicalTrials.gov NCT00391872) was conducted from October 2006 to February 2009 and randomly assigned 18 624 patients with ST-segment–elevation myocardial infarction (MI), non-ST–segment elevation MI, or unstable angina, treated with an invasive or a noninvasive approach, to receive either ticagrelor or clopidogrel as soon as possible after admission. Details of study design, patients, outcome definitions, and results have been described elsewhere.[22] In brief, ticagrelor was administered as a 180-mg loading dose followed by 90 mg twice daily. Patients assigned to clopidogrel received a maintenance dose of 75 mg daily. Those who were clopidogrel naïve were also administered a 300- to 600-mg loading dose. All patients received aspirin unless intolerant. The randomized treatment continued for a minimum of 6 to a maximum of 12 months (median duration 9.1 months). The primary efficacy end point was a composite of cardiovascular death, MI, or stroke. The primary safety end point was all major bleeding according to PLATO definition. Bleeding events were also defined according to the Thrombolysis In Myocardial Infarction (TIMI) and Global Use of Strategies to Open Occluded Arteries (GUSTO) classifications.[22]

Patients randomized in PLATO with available DM and CKD status at the time of randomization were included in the present analysis. Accordingly, patients were classified into 4 groups: DM+/CKD+, DM+/CKD−, DM−/CKD+, and DM−/CKD−. DM status was defined by the investigators at the time of randomization. Serum glucose and hemoglobin A1c were also measured and used to further characterize the study population, with poor glycemic control defined as levels above the median of serum glucose (6.8 mmol/L) and the median of percentage hemoglobin A1c (6.0%).[23] CKD was defined as a creatinine clearance (CrCl) <60 mL/min according to the Cockcroft-Gault equation.[24] There were no exclusion criteria for renal dysfunction in the PLATO trial except for the requirement of dialysis. In an exploratory analysis, CKD status was also stratified according to the Modification of Diet in Renal Disease and Chronic Kidney Disease Epidemiology

Collaboration equations.[25] In addition, in a subgroup of patients (n=13 688), kidney function was assessed based on cystatin C levels measured on stored samples using the Creatinine-Cystatin C Chronic Kidney Disease Epidemiology Collaboration equation.[26]

The PLATO trial adhered to the Declaration of Helsinki and was approved by the appropriate ethical review boards. All patients provided written informed consent. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Statistical Analysis

Categorical baseline variables are presented as frequencies and percentages and compared by DM/CKD group using χ^2 tests. Continuous baseline variables are presented as medians and 25th to 75th percentiles and compared by DM/CKD group using Kruskal–Wallis tests. Kaplan–Meier estimated event rates from randomization to 12 months were plotted by DM/CKD groups. Cox proportional hazards models were used to assess the associations between CKD-DM status and clinical end points. Multivariable Cox regression models included randomized treatment, age, sex, body mass index, heart rate, prior MI, hypertension, dyslipidemia, smoking status, previous percutaneous coronary intervention or coronary artery bypass graft (CABG), and type of ACS as covariates. The interaction between DM/CKD status and randomized treatment was examined by adding an interaction term to the model. Results are presented as adjusted hazard ratios (HR) with 95% CI. In the comparisons between DM/CKD groups, HRs are reported using DM−/CKD− group as reference. All statistical analyses were performed with SAS 9.4 (SAS Institute, Cary, NC). A 2-sided *P* value of <0.05 was considered statistically significant for differences between groups and treatments.

Results

Patients and Outcomes According to CKD and DM Status

Among patients randomized in the PLATO trial, 15 108 had DM and CKD status available and were classified as follows: DM+/CKD+ (n=1058), DM+/CKD− (n=2748), DM−/CKD+ (n=2160), and DM−/CKD− (n=9142). Baseline characteristics are reported in Table 1. After excluding patients who prematurely discontinued because of death, the number of patients who discontinued treatment during follow-up was low (43 in the CKD+DM+ group [0.28%], 71 in the CKD−DM+ group [0.47%], 83 in the CKD+DM− group [0.55%], and 206 in the CKD−DM− group [1.36%]). Patients with DM+/CKD+ more frequently had a prior history of cardiovascular disease, including MI, stroke, and peripheral arterial disease; were more frequently diagnosed with non-ST-elevation ACS rather than ST-elevation MI; and were more frequently treated with a noninvasive approach.

Patients with DM+/CKD+ had an over 3-fold higher incidence of the primary end point at 12 months compared with DM−/CKD− patients (23.3% versus 7.1%; adjusted HR 2.22; 95% CI 1.88–2.63). Patients with DM+/CKD− (10.7%; adjusted HR 1.34; 95% CI 1.16–1.55) and DM−/CKD+ (15.8%; adjusted HR 1.60; 95% CI 1.37–1.86) had an intermediate risk profile (*P* for trend <0.001; Figure 1). The same trend was shown for the individual components of the primary end point, cardiovascular death, MI, and stroke, as well as for all-cause mortality (Figure 2). Patients with DM+/CKD+ also had the highest risk of PLATO-defined major bleeding compared with DM−/CKD− patients (14.8% versus 8.5%; adjusted HR 1.47; 95% CI 1.21–1.77) and patients with DM+/CKD− (11.7%; adjusted HR 1.34; 95%; CI: 1.17–1.54) or DM−/CKD+ (11.8%; adjusted HR 1.13; 95% CI 0.96–1.33) (Figure 3A). Non-CABG-related major bleeding rates were higher in patients with DM+/CKD+ and DM−/CKD+ compared with patients with DM+/CKD− and DM−/CKD− (Figure 3B). Major bleeding defined according to TIMI and GUSTO criteria showed a similar trend (Figure 4). Results were consistent when measures of poor glycemic control and alternative definitions of CKD were considered (Table 2).

Outcomes of Ticagrelor Versus Clopidogrel According to CKD and DM Status

Compared with clopidogrel, ticagrelor significantly reduced the incidence of the primary end point consistently across subgroups (*P* interaction=0.3). However, the absolute risk reduction (ARR) with ticagrelor versus clopidogrel was considerably higher in DM+/CKD+ patients (11.26%; adjusted HR 0.78; 95% CI 0.61–1.01) compared with DM−/CKD− (1.37%; adjusted HR 0.86; 95% CI 0.73–1.00) (Figures 5 and 6). Consistent findings were shown on all the components of the primary end point (Table 3). In particular, ticagrelor led to a 5.8% ARR in cardiovascular death in patients with DM+/CKD+ compared with a 0.2% reduction in DM−/CKD− patients. Accordingly, the number-needed-to-treat for the primary end point was 8.9 in DM+/CKD+ and 73 in DM−/CKD−, and for cardiovascular death 17.2 in DM+/CKD+ and 500 in DM−/CKD−.

The effects of ticagrelor versus clopidogrel on PLATO-defined major bleeding were consistent across subgroups (*P* interaction=0.3). In particular, there was no increased risk of major bleeding with ticagrelor compared with clopidogrel in the subgroup of patients with DM+/CKD+ (27.4% versus 26.9%; HR 1.02; 95% CI 0.75–1.40). Accordingly, the effects

Table 1. Baseline Characteristics by DM/CKD Status

Group of Characteristics	Characteristic (at Baseline)	DM+/CKD+ (n=1058)	DM+/CKD− (n=2748)	DM−/CKD+ (n=2160)	DM−/CKD− (n=9142)	*P* Value
Demographics	Age (y), median (Q1–Q3)	72 (66–78)	61 (55–68)	74 (68–79)	59 (52–66)	<0.0001
	Age ≥75 y	429 (40.5%)	233 (8.5%)	1060 (49.1%)	604 (6.6%)	<0.0001
	Female sex	456 (43.1%)	851 (31.0%)	823 (38.1%)	2176 (23.8%)	<0.0001
	Weight (kg), median (Q1–Q3)	75 (65–84)	84 (74–95)	72 (62–80)	80 (70–90)	<0.0001
	Weight <60 kg	107 (10.1%)	120 (4.4%)	349 (16.2%)	498 (5.4%)	<0.0001
	Height (cm), median (Q1–Q3)	165 (160–172)	170 (163–175)	167 (160–173)	171 (165–177)	<0.0001
	BMI (kg/m^2), median (Q1–Q3)	26.9 (24.6–30.2)	29.3 (26.4–32.9)	25.4 (23.2–28.1)	27.4 (24.8–30.2)	<0.0001
	Waist circumference (cm), median (Q1–Q3)	99 (91–108)	103 (94–112)	95 (86–102)	97 (90–105)	<0.0001
Race, n (%)	White	922 (87.1)	2515 (91.5)	1928 (89.3)	8553 (93.6)	<0.0001
	Black	22 (2.1)	46 (1.7)	28 (1.3)	71 (0.8)	
	Asian	84 (7.9)	160 (5.8)	160 (7.4)	457 (5.0)	
	Other	30 (2.8)	27 (1.0)	44 (2.0)	61 (0.7)	
Cardiovascular risk factors, n (%)	Habitual smoker	130 (12.3)	800 (29.1)	413 (19.1)	4061 (44.4)	<0.0001
	Hypertension	925 (87.4)	2162 (78.7)	1574 (72.9)	5187 (56.7)	<0.0001
	Dyslipidemia	622 (58.8)	1629 (59.3)	916 (42.4)	3816 (41.7)	<0.0001
History, n (%)	Angina pectoris	651 (61.5)	1423 (51.8)	1137 (52.6)	3647 (39.9)	<0.0001
	Myocardial infarction	360 (34.0)	676 (24.6)	556 (25.7)	1507 (16.5)	<0.0001
	Congestive heart failure	176 (16.6)	188 (6.8)	229 (10.6)	255 (2.8)	<0.0001
	PCI	217 (20.5)	462 (16.8)	290 (13.4)	1025 (11.2)	<0.0001
	CABG	139 (13.1)	236 (8.6)	155 (7.2)	350 (3.8)	<0.0001
	TIA	48 (4.5)	75 (2.7)	81 (3.8)	191 (2.1)	<0.0001
	Nonhemorrhagic stroke	96 (9.1)	129 (4.7)	117 (5.4)	242 (2.6)	<0.0001
	Peripheral arterial disease	149 (14.1)	210 (7.6)	163 (7.5)	422 (4.6)	<0.0001
Medications on arrival, n (%)	Aspirin	1007 (95.2)	2618 (95.3)	2033 (94.1)	8756 (95.8)	0.01
	β-Blockade	842 (79.6)	2257 (82.1)	1613 (74.7)	6739 (73.7)	<0.0001
	ACE-inhibition and/or ARB	806 (76.2)	2049 (74.6)	1397 (64.7)	5361 (58.6)	<0.0001
	Statin	823 (77.8)	2230 (81.1)	1651 (76.4)	7350 (80.4)	<0.0001
	Ca-inhibitor	276 (26.1)	539 (19.6)	352 (16.3)	1054 (11.5)	<0.0001
	Diuretic	497 (47.0)	793 (28.9)	758 (35.1)	1449 (15.8)	<0.0001
	Insulin treatment before admission	282 (26.7)	572 (20.8)			0.0001
Medications index event to discharge, n (%)	GP 2b/3a inhibitor	177 (16.7)	734 (26.7)	413 (19.1)	2686 (29.4)	<0.0001
	Unfractionated heparin	524 (49.5)	1591 (57.9)	1195 (55.3)	5473 (59.9)	<0.0001

Continued

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Table 1. Continued

Group of Characteristics	Characteristic (at Baseline)	DM+/CKD+ (n=1058)	DM+/CKD− (n=2748)	DM−/CKD+ (n=2160)	DM−/CKD− (n=9142)	*P* Value
	Low-molecular-weight heparin	590 (55.8)	1460 (53.1)	1199 (55.5)	4734 (51.8)	0.003
	Fondaparinux	34 (3.2)	74 (2.7)	74 (3.4)	249 (2.7)	0.3
	Bivalirudin	25 (2.4)	90 (3.3)	34 (1.6)	158 (1.7)	<0.0001
Intended approach	Invasive	603 (57.0%)	1912 (69.6%)	1311 (60.7%)	6915 (75.6%)	<0.0001
	Noninvasive	455 (43.0%)	836 (30.4%)	849 (39.3%)	2227 (24.4%)	
Final ACS diagnosis	ST-elevation MI	244 (23.1%)	863 (31.4%)	638 (29.6%)	3980 (43.6%)	<0.0001
	Non-ST-elevation MI	559 (52.9%)	1259 (45.8%)	1038 (48.2%)	3622 (39.6%)	
	Unstable angina	224 (21.2%)	566 (20.6%)	427 (19.8%)	1336 (14.6%)	
	Other	29 (2.7%)	60 (2.2%)	50 (2.3%)	199 (2.2%)	
Randomized treatment	Delay from start of pain (h), median (Q1–Q3)	14.2 (6.8–21.2)	12.7 (5.7–20.4)	14.0 (5.8–21.1)	10.2 (4.3–19.0)	<0.0001
	Treatment duration (d), median (Q1–Q3)	258 (55–361)	276 (179–365)	265 (73–363)	284 (184–366)	<0.0001
Biomarkers	Creatinine (μmol/L), median (Q1–Q3)	115.0 (106.0–141.0)	80.0 (70.7–88.0)	106.0 (97.0–124.0)	80.0 (71.0–88.0)	<0.0001
	Glucose (mmol/L), median (Q1–Q3)	9.9 (7.2–13.5)	9.7 (7.2–13.2)	6.5 (5.6–7.9)	6.4 (5.6–7.7)	<0.0001
	HbA1c (mmol/mol), median (Q1–Q3)	7.5 (6.6–8.7)	7.6 (6.7–9.1)	5.9 (5.6–6.2)	5.8 (5.6–6.1)	<0.0001
	Hemoglobin (mmol/mol), median (Q1–Q3)	128.0 (116.0–140.0)	139.0 (128.0–149.0)	134.0 (123.0–145.0)	142.0 (132.0–151.0)	<0.0001
	NT-proBNP (pmol/L), median (Q1–Q3)	1734 (610.0–4071)	395.0 (146.0–953.0)	1002 (320.0–2544)	277.0 (99.0–721.0)	<0.0001
	Troponin I μg/L, median (Q1–Q3)	1.10 (0.12–6.00)	0.95 (0.11–4.30)	1.00 (0.11–5.70)	0.90 (0.12–4.70)	0.01
	Creatinine (mg/dL), median (Q1–Q3)	1.3 (1.2–1.6)	0.9 (0.8–1.0)	1.2 (1.1–1.4)	0.9 (0.8–1.0)	<0.0001
	CrCl (mL/min), median (Q1–Q3)	48.4 (38.9–55.1)	86.7 (73.2–104.5)	50.3 (42.7–55.9)	87.7 (74.5–104.0)	<0.0001

ACE indicates angiotensin converting enzyme; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; CKD, chronic kidney disease; CrCl, creatinine clearance by Cockcroft-Gault equation; DM, diabetes mellitus; GP, glycoprotein; HbA1c, hemoglobin A1c; MI, myocardial infarction; NT-proBNP, N-terminal pro-brain natriuretic peptide; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

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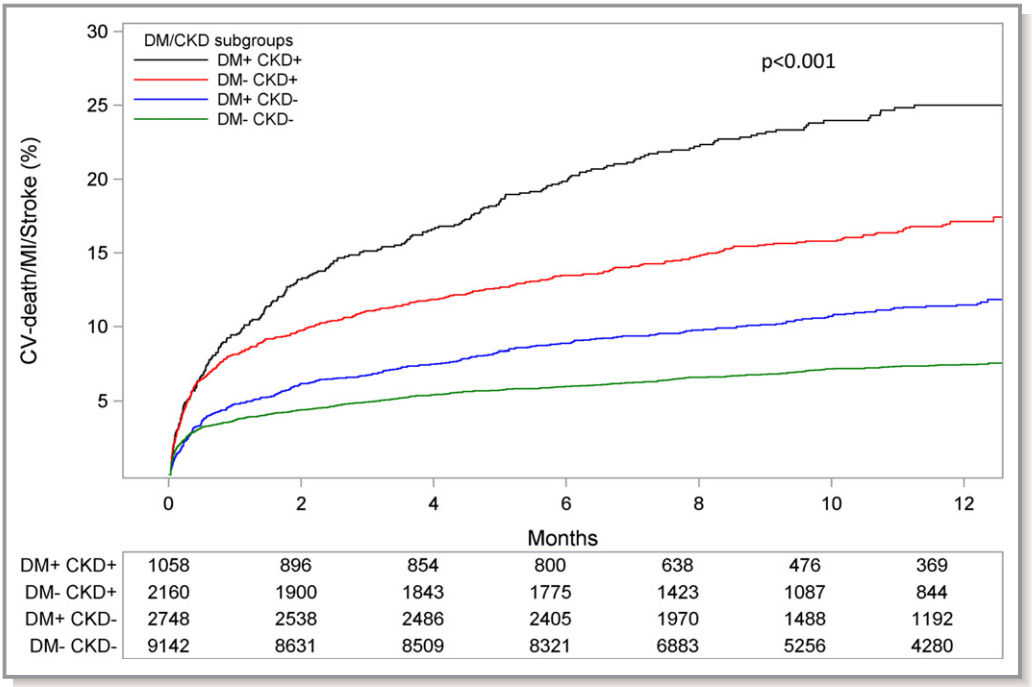

Figure 1. Kaplan–Meier event rate curves for the cumulative incidence of the primary composite end point of cardiovascular (CV) death, myocardial infarction (MI), and stroke stratified by DM/CKD status. *P* value represents the overall comparison among groups according to DM/CKD status. The model is adjusted for age, sex, body mass index, heart rate, prior myocardial infarction, hypertension, dyslipidemia, angina pectoris, smoking status, previous percutaneous coronary intervention or coronary artery bypass graft, type of acute coronary syndrome and randomized treatment. CKD indicates chronic kidney disease; DM, diabetes mellitus.

on non-CABG-related major bleeding were also consistent regardless of CKD/DM status, although the increase in bleeding risk with ticagrelor was numerically higher in patients with CKD (both DM+/CKD+ and DM−/CKD+) (Table 3). The number-needed-to-harm for all major bleeding was 208 in DM+/CKD+ and 49 in DM−/CKD− and for non-CABG-related major bleeding was 73 in DM+/CKD+ and 105 in DM−/CKD−. Major bleeding defined according to TIMI and GUSTO criteria followed the same trend (Table 4).

Results were consistent when measures of poor glycemic control and alternative definitions of CKD were considered. In particular, with poor glycemic control defined by hemoglobin A1c and CKD defined by the Creatinine-Cystatin C Chronic Kidney Disease Epidemiology Collaboration equation, the effects of ticagrelor versus clopidogrel on ischemic and bleeding events were consistent across subgroups (Table 5). In patients with DM+/CKD+, ticagrelor led to a 14% ARR in the primary end point and a 9% ARR in cardiovascular death compared with clopidogrel with no significant increase in major bleeding.

Discussion

The data from the present post hoc analysis of the PLATO trial represent the largest exploring the impact of having DM, CKD, or both, on clinical outcomes in ACS patients. Our study showed that (1) the concomitant presence of CKD and DM is not uncommon in patients with ACS, representing 7% of the overall study population; (2) patients with CKD and DM are more likely to already have established atherosclerotic disease, more frequently present with a non-ST-elevation ACS and are more likely to be treated with a noninvasive approach; (3) patients with either DM or CKD are at increased risk of ischemic events compared with patients without these risk factors; and the combination of DM and CKD status is associated with an over 3-fold increased risk of ischemic events compared with patients without these risk factors, including a 6-fold increase in cardiovascular death; (4) the presence of DM and CKD is associated with a significant increase in major bleeding and non-CABG-related major bleeding, but not in CABG-related bleeding; (5) the benefit of ticagrelor over clopidogrel on ischemic outcomes is consistent across DM and CKD status, but the magnitude of absolute benefit is enhanced in higher-risk patients; in particular, in patients with DM and CKD ticagrelor led to a 22% relative risk reduction and an 11% ARR in the primary end point compared with clopidogrel, including a 21% relative risk reduction and an 5.8% ARR in cardiovascular death; and (6) there was no signal of increased risk of bleeding with ticagrelor in patients with CKD and DM as compared with the other subgroups.

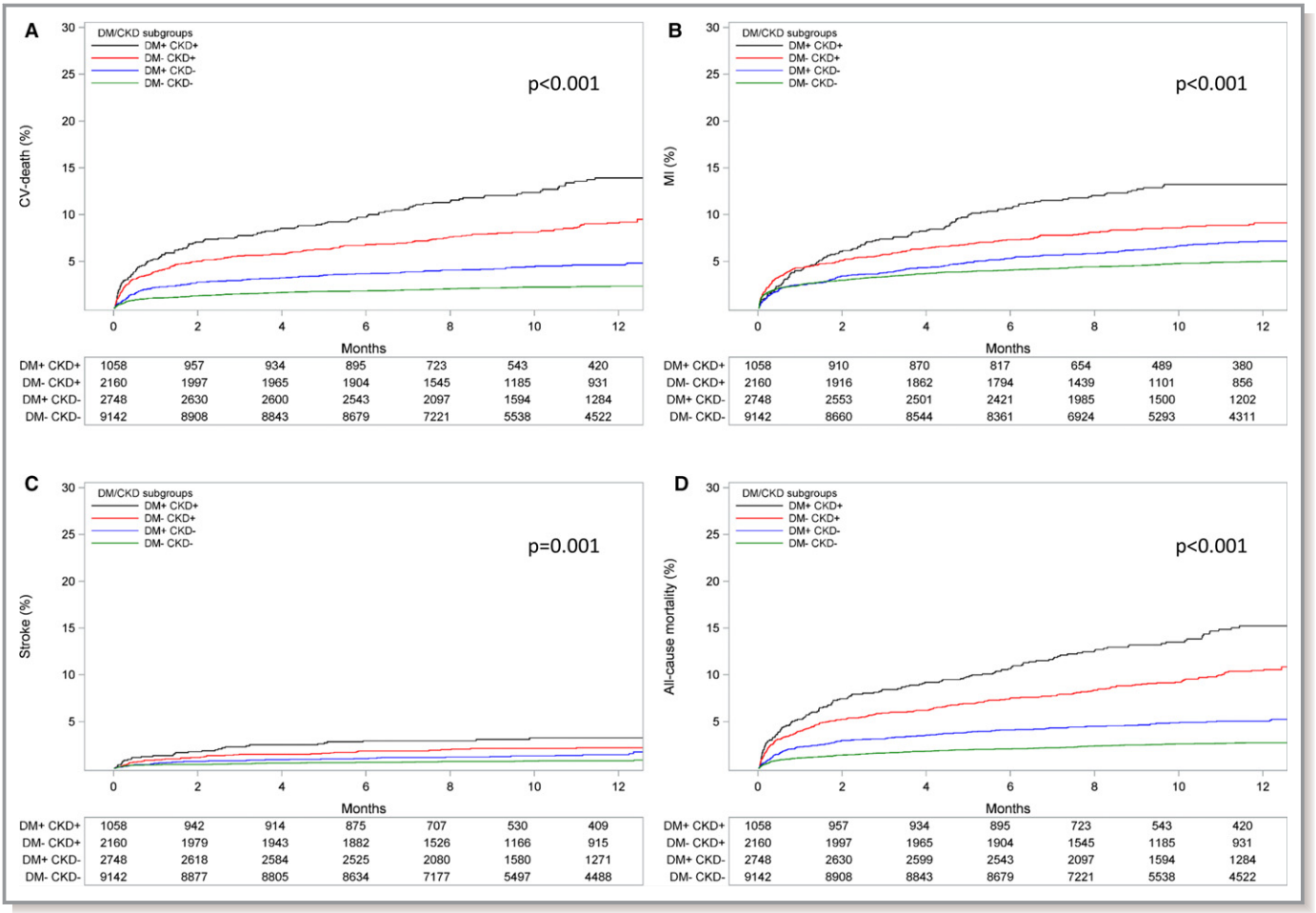

Figure 2. Kaplan–Meier event rate curves for the cumulative incidence of (**A**) cardiovascular (CV) death, (**B**) myocardial infarction (MI), (**C**) stroke, and (**D**) all-cause mortality stratified by DM/CKD status. *P* value represents the overall comparison among groups according to DM/CKD status. The model is adjusted for age, sex, body mass index, heart rate, prior myocardial infarction, hypertension, dyslipidemia, angina pectoris, smoking status, previous percutaneous coronary intervention or coronary artery bypass graft, type of acute coronary syndrome, and randomized treatment. CKD indicates chronic kidney disease; DM, diabetes mellitus.

DM and CKD have both been independently associated with an increased risk of cardiovascular events, which may be attributed to abnormalities specific to these patients favoring a prothrombotic and pro-inflammatory status.[1,2] Among patients with DM, impaired clopidogrel-induced antiplatelet effects leading to high levels of platelet reactivity has been largely attributed to an attenuation of clopidogrel's pharmacokinetic profile, characterized by lower active metabolite levels, and in part to dysregulation of the $P2Y_{12}$ receptor signaling pathway.[9,10,27] Subgroup analysis of major clinical trials have shown a reduced benefit of clopidogrel in CKD patients.[2] Patients with CKD are characterized by upregulation of the $P2Y_{12}$ signaling pathway induced by dinucleoside polyphosphates and impaired hepatic function, which can potentially impact clopidogrel metabolism.[28–32] However, while pharmacodynamic studies have consistently shown DM to be associated with impaired clopidogrel-induced antiplatelet effects, results have been conflicting when assessing how CKD affects clopidogrel response. These observations may be attributed to confounders within the heterogeneous study populations in which these studies have been performed.[12–19] Pharmacodynamic assessments specifically conducted among DM patients who also have CKD have shown these patients to have greater impairment of clopidogrel-induced platelet inhibition compared with those without CKD.[13,15,16] However, in the absence of DM, renal function has not always been shown to affect clopidogrel's antiplatelet effects.[12,13,17–19] Overall, these findings suggest that there may be some level of synergism of DM and CKD on platelet reactivity in clopidogrel-treated patients, which would be in line with the clinical observations of the present investigation.[16]

A post hoc analysis of the FREEDOM (Comparison of Two Treatments for Multivessel Coronary Artery Disease in Individuals With Diabetes) trial assessing revascularization strategies (surgical versus percutaneous) among DM patients (n=1843) with multivessel coronary artery disease

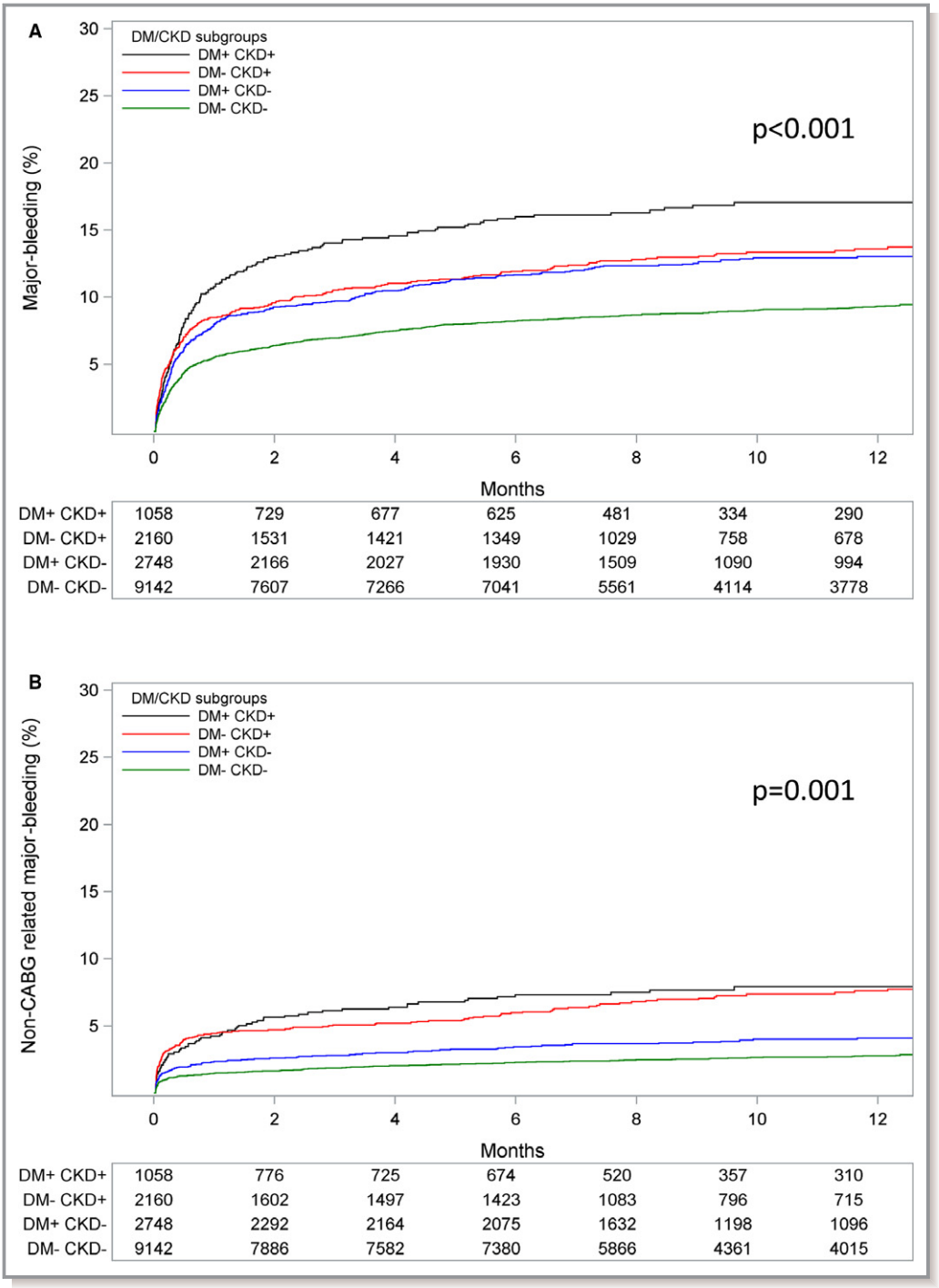

Figure 3. Kaplan–Meier event rate curves for the cumulative incidence of (**A**) major bleeding, and (**B**) non-CABG-related major bleeding stratified by DM/CKD status. *P* value represents the overall comparison among groups according to DM/CKD status. Bleeding is defined according to PLATO criteria. The model is adjusted for age, sex, body mass index, heart rate, prior myocardial infarction, hypertension, dyslipidemia, angina pectoris, smoking status, previous percutaneous coronary intervention, or coronary artery bypass graft, type of acute coronary syndrome, and randomized treatment. CABG indicates coronary artery bypass graft; CKD, chronic kidney disease; DM, diabetes mellitus; PLATO, Platelet Inhibition and Patient Outcomes.

evaluated the impact of CKD status on clinical outcomes.[20] In this analysis, CKD affected clinical outcomes irrespective of the strategy used for revascularization, leading to a nearly 2-fold risk increase in all-cause mortality, cardiovascular death, and stroke and a 1.5-fold risk increase in major bleeding.[20] Our analysis represents the largest data set to

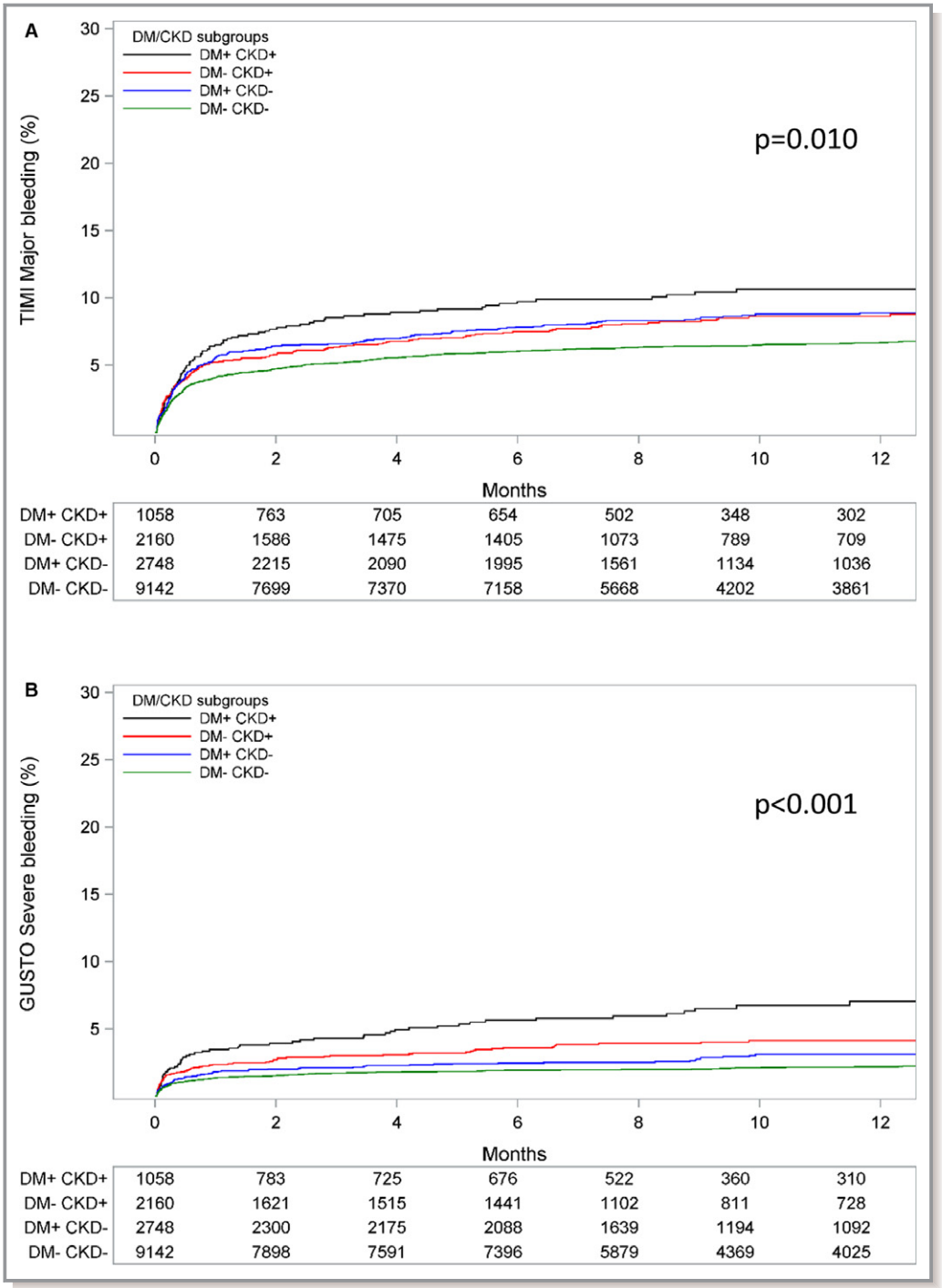

Figure 4. Kaplan–Meier event rate curves for the cumulative incidence of major/severe bleeding according to (**A**) TIMI, and (**B**) GUSTO criteria stratified by DM/CKD status. *P* value represents the overall comparison among groups according to DM/CKD status. The model is adjusted for age, sex, body mass index, heart rate, prior myocardial infarction, hypertension, dyslipidemia, angina pectoris, smoking status, previous percutaneous coronary intervention or coronary artery bypass graft, type of acute coronary syndrome, and randomized treatment. CKD indicates chronic kidney disease; DM, diabetes mellitus; GUSTO, Global Use of Strategies to Open Occluded Arteries; TIMI, thrombolysis in myocardial infarction.

unravel the contributing role of DM and CKD on cardiovascular outcomes. We extend the findings from the FREEDOM analysis to ACS patients receiving dual antiplatelet therapy undergoing different treatment strategies (invasive or noninvasive), showing that the presence of either DM or CKD increases long-term cardiovascular events to a similar

Table 2. Ischemic and Bleeding Outcomes According to DM/CKD Subgroup, With Poor Glycemic Control Defined by HbA1c and CKD Defined by the Creatinine-Cystatin C CKD-EPI Equation

DM/CKD Subgroup	No. of Events	No. of Patients	Event Rate (%)*	HR (95% CI)†	*P* Value‡
Cardiovascular death/MI/stroke					
DM−/CKD−	392	1264	6.9		<0.0001
DM+/CKD−	580	5726	10.1	1.33 (1.16–1.52)	
DM−/CKD+	123	734	16.8	1.72 (1.39–2.13)	
DM+/CKD+	263	1264	20.8	2.09 (1.76–2.49)	
Cardiovascular death					
DM−/CKD−	121	5673	2.1		<0.0001
DM+/CKD−	215	5726	3.8	1.54 (1.23–1.94)	
DM−/CKD+	65	734	8.9	2.50 (1.81–3.44)	
DM+/CKD+	155	1264	12.3	3.44 (2.64–4.48)	
MI					
DM−/CKD−	258	5673	4.5		<0.0001
DM+/CKD−	357	5726	6.2	1.24 (1.05–1.47)	
DM−/CKD+	69	734	9.4	1.60 (1.21–2.12)	
DM+/CKD+	130	1264	10.3	1.66 (1.32–2.10)	
All-cause death					
DM−/CKD−	145	5673	2.6		<0.0001
DM+/CKD−	238	5726	4.2	1.45 (1.17–1.79)	
DM−/CKD+	72	734	9.8	2.21 (1.63–2.99)	
DM+/CKD+	174	1264	13.8	3.19 (2.49–4.08)	
Stroke					
DM−/CKD−	46	5673	0.8		0.1679
DM+/CKD−	74	5726	1.3	1.43 (0.98–2.08)	
DM−/CKD+	11	734	1.5	1.15 (0.58–2.29)	
DM+/CKD+	27	1264	2.1	1.67 (0.99–2.81)	
Major bleeding					
DM−/CKD−	484	5673	8.5		0.0039
DM+/CKD−	629	5726	11.0	1.26 (1.11–1.42)	
DM−/CKD+	86	734	11.7	1.14 (0.90–1.45)	
DM+/CKD+	148	1264	11.7	1.14 (0.94–1.39)	
Non-CABG-related major bleeding					
DM−/CKD−	161	5673	2.8		0.0070
DM+/CKD−	180	5726	3.1	1.00 (0.81–1.25)	
DM−/CKD+	44	734	6.0	1.34 (0.94–1.91)	
DM+/CKD+	88	1264	7.0	1.55 (1.16–2.07)	
CABG-related major bleeding					
DM−/CKD−	367	5628	6.5		0.1678
DM+/CKD−	366	5673	6.5	1.02 (0.88–1.18)	
DM−/CKD+	44	727	6.1	0.96 (0.69–1.32)	
DM+/CKD+	96	1250	7.7	1.29 (1.01–1.65)	

The model is adjusted for age, sex, BMI, heart rate, prior myocardial infarction, hypertension, dyslipidemia, angina pectoris, smoking status, previous PCI or CABG, type of ACS define and randomized treatment. BMI indicates body mass index; CABG, coronary artery bypass graft; CKD, chronic kidney disease; CKD-EPI, chronic kidney disease epidemiology collaboration; DM, diabetes mellitus; HbA1c, hemoglobin A1c; HR, hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention.

*The crude event rate, (no. events/no. of subjects)×100%.

†Subgroup DM−/CKD− is the reference category.

‡*P* value for the effect of DM/CKD subgroup.

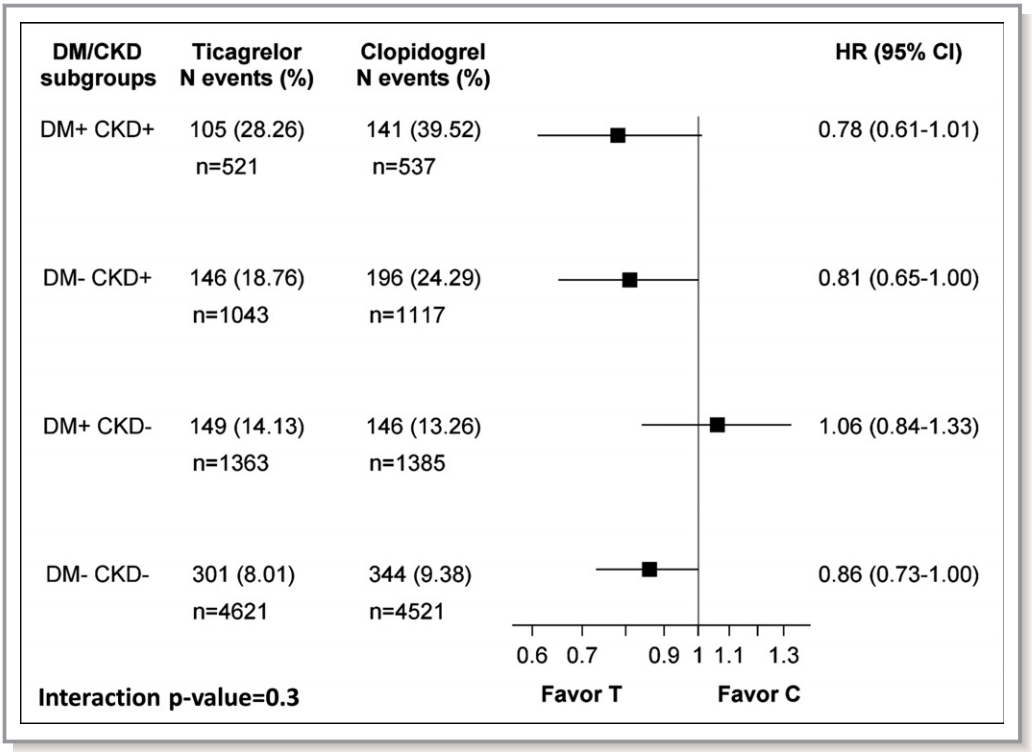

Figure 5. Hazard ratios (HR) with 95% CI for the primary composite end point (cardiovascular death, myocardial infarction, and stroke) of ticagrelor (T) vs clopidogrel (C) stratified by DM/CKD status. The model is adjusted for age, sex, body mass index, heart rate, prior myocardial infarction, hypertension, dyslipidemia, angina pectoris, smoking status, previous percutaneous coronary intervention or coronary artery bypass graft, type of acute coronary syndrome, and randomized treatment. CKD indicates chronic kidney disease; DM, diabetes mellitus.

extent but when these risk factors are combined, this risk is further amplified. Notably, this was consistent using multiple definitions of DM and CKD, supporting the validity of our study findings. The ever-rising prevalence of both DM and CKD underscore the relevance of these observations. In fact, both clinical disorders are pandemic public health problems. CKD has a prevalence of 13% in the United States and up to 17% in Europe.[3,33] Importantly, DM is a key risk factor for the development of CKD, and about one third of DM patients are found to have CKD.[3] Therefore, with the increasing prevalence of DM, which is expected to double over the next 20 years, the prevalence of CKD is also expected to rise.[34] These observations underscore the need for defining the most effective treatment options for these high-risk patients, including strategies to reduce the risk of developing CKD in patients with DM. To this extent, sodium-glucose cotransporter-2 inhibitors are new antihyperglycemic therapies known to reduce long-term decline in kidney function.[35,36] Similarly, in patients with established CKD, glucose control is also critical to reduce the risk of developing DM.

Ticagrelor is characterized by more potent and predictable antiplatelet effects compared with clopidogrel, which translate into better clinical outcomes in ACS patients, albeit at the expense of an increased risk of major bleeding.[22,37] Pharmacodynamic assessments have shown that the enhanced potency of ticagrelor over clopidogrel persists in patients with DM,[38,39] and in the DM subgroup of PLATO, compared with clopidogrel, ticagrelor was associated with a 2.1% ARR in the primary end point, a finding that was consistent with the overall trial results (*P*-interaction: 0.49).[23] In patients with CKD, ticagrelor led to a 4.7% ARR of the primary ischemic end point, which was also consistent with the overall trial results (*P*-interaction: 0.13).[24] However, there are limited data on the pharmacodynamic effects of ticagrelor in CKD patients.[40,41] The present study findings show that, although the benefit of ticagrelor over clopidogrel is consistent across subgroups (*P*-interaction: 0.264), the enhanced benefit of ticagrelor in patients with CKD is even greater in patients who also have DM (11% ARR), including a 5.8% ARR in cardiovascular mortality. Indeed, the higher event rates that characterize these patients can contribute to the greater magnitude of the treatment effect associated with more potent platelet $P2Y_{12}$ inhibition induced by ticagrelor. In addition, prior investigations supporting impaired clopidogrel-induced platelet inhibition in DM patients, in particular those

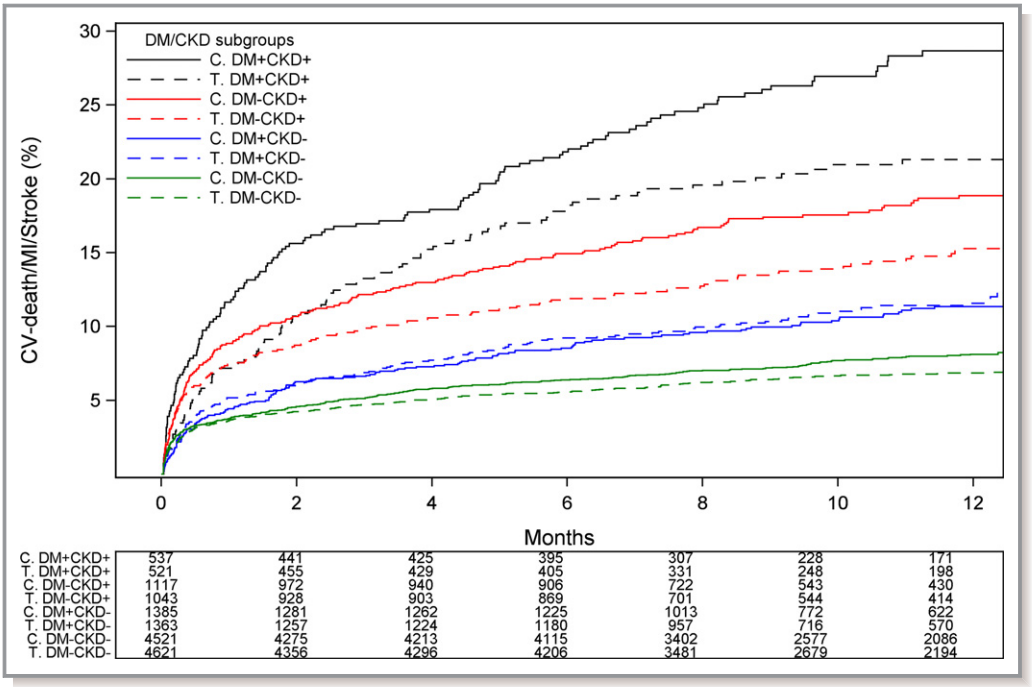

Figure 6. Kaplan–Meier event rate curves for the cumulative incidence of the primary composite end point of cardiovascular (CV) death, myocardial infarction, and stroke stratified by treatment group and DM/CKD status. C indicates clopidogrel; CKD, chronic kidney disease; DM, diabetes mellitus; T, ticagrelor.

also with CKD, may contribute to these findings.[9–12,14,16,17] However, because DM and CKD patients are characterized by enhanced vascular inflammation and endothelial dysfunction, it cannot be excluded that they could be more susceptible to the off-target effects of ticagrelor. In fact, ticagrelor increases adenosine levels by inhibiting its reuptake by erythrocytes and adenosine may modulate inflammatory response and favor vasodilation.[42]

Patients with CKD and DM are overall at increased risk of bleeding. This may explain why in some studies these patients are less commonly treated with more potent platelet-inhibiting therapies.[43,44] The increased risk for bleeding among DM and CKD patients was also confirmed in this analysis. However, there was no increased risk of major bleeding with ticagrelor versus clopidogrel in the subgroup of patients with DM+/CKD+. The increase in non-CABG-related major bleeding events was numerically higher in patients with DM+/CKD+, but the relative risk was similar and the effect was overall consistent across groups, also using different bleeding definitions. These findings were also consistent using multiple definitions of DM and CKD.

Study Limitations

The results of the present study should be interpreted in light of some limitations. Patients with end-stage renal disease requiring hemodialysis were excluded from the trial; therefore, our results are not applicable to this setting. Although we used different definitions to define CKD status, we did not measure albumin–creatinine ratio and therefore may have underestimated the true prevalence of CKD. Accordingly, the number of patients with CKD+ in our study population was relatively small. CKD was defined according to baseline creatinine levels at the time of ACS presentation. Therefore, creatinine clearance may not be reflective of steady-state kidney function. Indeed, it may be argued that the results of our study pertain to a cohort of CKD patients with mostly moderate (stage 3) degree of renal impairment and the results cannot be extrapolated to those with more advanced stages of renal disease. Moreover, the present investigation does not provide any mechanistic insights for the enhanced rates of adverse outcomes and the inconsistent response to different classes of $P2Y_{12}$ inhibiting therapies among patients with concomitant DM and CKD, which is a topic of ongoing investigation (NCT02539160). It may be argued that there are large baseline differences between the DM/CKD groups that might not be possible to fully account for by covariate adjustment. Although an age/sex/comorbid matched analysis could have represented an option, this typically leads to loss of information when not all subjects can be matched, and a similar analysis would have resulted in smaller patient cohorts and ultimately not reflective of risk profile of this patient population in real-world clinical practice. Finally, our results derive from a post hoc subgroup analysis and should

Table 3. Outcomes of Ticagrelor Versus Clopidogrel According to DM/CKD Status

DM/CKD Subgroup	Ticagrelor Patients (N)	Clopidogrel Patients (N)	Ticagrelor Event Rate, N (%)	Clopidogrel Event Rate, N (%)	HR (95% CI)	*P* Value Interaction
Cardiovascular death						0.3
DM+/CKD+	521	537	55 (13.60)	77 (19.40)	0.79 (0.55–1.11)	
DM−/CKD+	1043	1117	69 (8.33)	111 (12.80)	0.68 (0.51–0.92)	
DM+/CKD−	1363	1385	59 (5.30)	62 (5.38)	1.00 (0.70–1.44)	
DM−/CKD−	4621	4521	98 (2.51)	104 (2.71)	0.93 (0.70–1.22)	
MI						0.2
DM+/CKD+	521	537	52 (13.79)	72 (19.66)	0.76 (0.53–1.09)	
DM−/CKD+	1043	1117	77 (9.77)	100 (12.29)	0.83 (0.62–1.12)	
DM+/CKD−	1363	1385	93 (8.76)	84 (7.58)	1.13 (0.84–1.52)	
DM−/CKD−	4621	4521	195 (5.16)	233 (6.33)	0.82 (0.67–0.99)	
All-cause death						0.5
DM+/CKD+	521	537	63 (15.58)	82 (20.66)	0.85 (0.61–1.18)	
DM−/CKD+	1043	1117	80 (9.66)	125 (14.41)	0.70 (0.53–0.93)	
DM+/CKD−	1363	1385	64 (5.75)	69 (5.98)	0.98 (0.70–1.37)	
DM−/CKD−	4621	4521	112 (2.87)	123 (3.21)	0.90 (0.69–1.16)	
Stroke						0.6
DM+/CKD+	521	537	13 (3.26)	18 (4.66)	0.78 (0.38–1.59)	
DM−/CKD+	1043	1117	23 (2.81)	20 (2.33)	1.24 (0.68–2.26)	
DM+/CKD−	1363	1385	22 (1.99)	16 (1.40)	1.42 (0.75–2.71)	
DM−/CKD−	4621	4521	40 (1.03)	31 (0.81)	1.28 (0.80–2.04)	
Major bleeding						0.3
DM+/CKD+	521	537	78 (27.37)	79 (26.89)	1.02 (0.75–1.40)	
DM−/CKD+	1043	1117	129 (21.73)	125 (19.42)	1.13 (0.88–1.44)	
DM+/CKD−	1363	1385	150 (17.61)	171 (18.88)	0.91 (0.73–1.13)	
DM−/CKD−	4621	4521	420 (13.23)	355 (11.19)	1.16 (1.01–1.34)	
Non-CABG-related major bleeding						0.7
DM+/CKD+	521	537	39 (12.87)	32 (10.18)	1.32 (0.82–2.10)	
DM−/CKD+	1043	1117	75 (12.15)	62 (9.14)	1.34 (0.96–1.88)	
DM+/CKD−	1363	1385	48 (5.30)	50 (5.13)	1.03 (0.69–1.52)	
DM−/CKD−	4621	4521	129 (3.88)	97 (2.93)	1.30 (1.00–1.69)	

The model is adjusted for age, sex, body mass index, heart rate, prior myocardial infarction, hypertension, dyslipidemia, angina pectoris, smoking status, previous percutaneous coronary intervention or CABG, type of acute coronary syndrome and randomized treatment. CABG indicates coronary artery bypass graft; CKD, chronic kidney disease; DM, diabetes mellitus; HR, hazard ratio; MI, myocardial infarction.

as such be considered as hypothesis-generating and requiring confirmation in prospectively designed studies.

Conclusions

In conclusion, the results of the present analysis showed that ACS patients with DM and CKD are at markedly increased risk for long-term atherothrombotic events compared with patients without these risk factors, as well as with those with only 1 of these. Although the ischemic benefit of ticagrelor versus clopidogrel was consistent in all patient subgroups, the magnitude of benefit was enhanced according to the patient risk profile. Although patients with DM and CKD are at increased risk of bleeding, there were no signals of increased risk of major bleeding events with ticagrelor. Overall, these data underscore the need for using more potent platelet-inhibiting therapy in ACS patients with DM and CKD who are often undertreated because of high perceived risk of bleeding.

Table 4. Bleeding Outcomes of Ticagrelor Versus Clopidogrel According to DM/CKD Status According to TIMI and GUSTO Criteria

DM/CKD Subgroup	Ticagrelor Patients (N)	Clopidogrel Patients (N)	Ticagrelor Event Rate, N (%)	Clopidogrel Event Rate, N (%)	HR (95% CI)	*P* Value Interaction
TIMI major bleeding						0.049
DM+/CKD+	521	537	48 (16.16)	48 (15.71)	1.02 (0.68–1.52)	
DM−/CKD+	1043	1117	78 (12.67)	81 (12.13)	1.05 (0.77–1.43)	
DM+/CKD−	1363	1385	93 (10.58)	124 (13.32)	0.77 (0.59–1.01)	
DM−/CKD−	4621	4521	308 (9.56)	252 (7.82)	1.21 (1.02–1.42)	
TIMI non-CABG-related major bleeding						0.219
DM+/CKD+	521	537	24 (7.84)	15 (4.71)	1.69 (0.89–3.23)	
DM−/CKD+	1043	1117	38 (6.01)	36 (5.22)	1.16 (0.74–1.83)	
DM+/CKD−	1363	1385	27 (2.95)	34 (3.47)	0.84 (0.51–1.40)	
DM−/CKD−	4621	4521	88 (2.63)	57 (1.71)	1.51 (1.08–2.11)	
GUSTO severe bleeding						0.882
DM+/CKD+	521	537	25 (8.12)	34 (10.88)	0.77 (0.46–1.28)	
DM−/CKD+	1043	1117	36 (5.72)	39 (5.70)	0.99 (0.63–1.56)	
DM+/CKD−	1363	1385	33 (3.63)	40 (4.09)	0.88 (0.55–1.39)	
DM−/CKD−	4621	4521	89 (2.67)	92 (2.78)	0.95 (0.71–1.27)	
GUSTO non-CABG-related severe bleeding						0.545
DM+/CKD+	521	537	20 (6.44)	19 (5.98)	1.08 (0.58–2.03)	
DM−/CKD+	1043	1117	25 (3.93)	25 (3.61)	1.06 (0.61–1.85)	
DM+/CKD−	1363	1385	17 (1.85)	25 (2.54)	0.74 (0.40–1.36)	
DM−/CKD−	4621	4521	54 (1.61)	41 (1.23)	1.28 (0.85–1.91)	

The model is adjusted for age, sex, BMI, heart rate, prior myocardial infarction, hypertension, dyslipidemia, angina pectoris, smoking status, previous PCI or CABG, type of ACS, and randomized treatment. ACS indicates acute coronary syndrome; BMI, body mass index; CABG, coronary artery bypass graft; CKD, chronic kidney disease; DM, diabetes mellitus; GUSTO, Global Use of Strategies to Open Occluded Arteries; HR, hazard ratio; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.

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This article is dedicated to the memory of the late Prof. Steen Husted.

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Table 5. Outcomes of Ticagrelor Versus Clopidogrel According to DM/CKD Status, With Poor Glycemic Control Defined by HbA1c and CKD Defined by the Creatinine-Cystatin C CKD-EPI Equation

DM/CKD Subgroup	Ticagrelor Patients (N)	Clopidogrel Patients (N)	Ticagrelor Event Rate, N (%)	Clopidogrel Event Rate, N (%)	HR (95% CI)	*P* Value Interaction
Cardiovascular death/MI/stroke						0.265
DM+/CKD+	633	631	105 (22.66)	158 (36.57)	0.68 (0.53–0.88)	
DM−/CKD+	344	390	49 (19.68)	74 (27.22)	0.77 (0.54–1.11)	
DM+/CKD−	2841	2886	267 (11.79)	313 (13.64)	0.87 (0.74–1.03)	
DM−/CKD−	2877	2797	191 (8.31)	201 (8.99)	0.92 (0.76–1.13)	
Cardiovascular death						0.257
DM+/CKD+	633	631	57 (11.52)	98 (20.70)	0.63 (0.45–0.87)	
DM−/CKD+	344	390	25 (9.42)	40 (13.63)	0.74 (0.45–1.23)	
DM+/CKD−	2841	2886	103 (4.34)	112 (4.62)	0.96 (0.73–1.25)	
DM−/CKD−	2877	2797	57 (2.39)	64 (2.75)	0.87 (0.61–1.24)	
MI						0.734
DM+/CKD+	633	631	53 (11.28)	77 (17.53)	0.71 (0.50–1.00)	
DM−/CKD+	344	390	29 (11.57)	40 (14.61)	0.84 (0.52–1.36)	
DM+/CKD−	2841	2886	165 (7.24)	192 (8.31)	0.87 (0.71–1.08)	
DM−/CKD−	2877	2797	124 (5.36)	134 (5.97)	0.89 (0.70–1.14)	
All-cause death						0.481
DM+/CKD+	633	631	68 (13.75)	106 (22.39)	0.70 (0.51–0.95)	
DM−/CKD+	344	390	28 (10.55)	44 (14.99)	0.74 (0.46–1.20)	
DM+/CKD−	2841	2886	113 (4.76)	125 (5.15)	0.94 (0.73–1.21)	
DM−/CKD−	2877	2797	64 (2.68)	81 (3.48)	0.77 (0.56–1.07)	
Stroke						0.293
DM+/CKD+	633	631	15 (3.08)	12 (2.57)	1.33 (0.62–2.85)	
DM−/CKD+	344	390	5 (1.90)	6 (2.06)	0.95 (0.29–3.12)	
DM+/CKD−	2841	2886	33 (1.40)	41 (1.70)	0.82 (0.52–1.30)	
DM−/CKD−	2877	2797	29 (1.22)	17 (0.73)	1.67 (0.92–3.05)	
Major bleeding						0.143
DM+/CKD+	633	631	74 (20.61)	74 (20.51)	1.03 (0.75–1.42)	
DM−/CKD+	344	390	43 (23.41)	43 (19.59)	1.12 (0.74–1.71)	
DM+/CKD−	2841	2886	307 (16.44)	322 (16.72)	0.97 (0.83–1.14)	
DM−/CKD−	2877	2797	272 (14.15)	212 (10.97)	1.28 (1.07–1.54)	
Non-CABG-related major bleeding						0.782
DM+/CKD+	633	631	48 (12.89)	40 (10.69)	1.29 (0.84–1.96)	
DM−/CKD+	344	390	23 (12.06)	21 (9.15)	1.36 (0.75–2.45)	
DM+/CKD−	2841	2886	93 (4.71)	87 (4.23)	1.12 (0.84–1.50)	
DM−/CKD−	2877	2797	95 (4.71)	66 (3.29)	1.39 (1.02–1.91)	

The model is adjusted for age, sex, BMI, heart rate, prior myocardial infarction, hypertension, dyslipidemia, angina pectoris, smoking status, previous PCI or CABG, type of ACS, and randomized treatment. ACS indicates acute coronary syndrome; BMI, body mass index; CABG, coronary artery bypass graft; CKD, chronic kidney disease; CKD-EPI, chronic kidney disease epidemiology collaboration; DM, diabetes mellitus; HR, hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention.

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SUPPLEMENTAL MATERIAL

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